TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
TM018RenzSel		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DE2004/002197	01.10.2004	02.10.2003

International Patent Classification (IPC) or national classification and IPC

C12N15/63,A61K48/00,C12N15/10

Applicant

PHILIPPS-UNIVERSITÄT MARBURG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-33 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-16 received by this Authority on 22.12.2005 with letter of 20.12.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/18-18/18 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☐ not complied with for the following reasons:

The claims submitted for international examination are not admissible under PCT Rule 13.1 for the following reasons:

The different inventions or groups of inventions are as follows:

1. Claims 1-8:
DNAzyme that specifically cleaves GATA-3 mRNA, drug and medical use

2. Claims 9-16:
DNAzyme that specifically cleaves t-bet mRNA, drug and medical use.

For the following reasons, these inventions or groups of inventions are not so linked as to form a single general inventive concept (PCT Rule 13.1):

The problem to be solved by both groups of inventions is that of providing DNAzymes that inhibit the mRNA of a transcription factor. The solutions relate to a GATA-3 mRNA-specific DNAzyme in the first invention, and to a T-bet mRNA-specific DNAzyme and its use in the second invention. Since the prior art already describes DNAzymes that inhibit transcription factors (WO 00/42173 and WO 01/11023), the groups of inventions are not linked by a common special technical feature. The independent claims of the three groups of inventions do not have a common special technical feature. Therefore, the present application does not satisfy the criterion of unity of invention pursuant to PCT Rule 13.1-13.3.

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-16	YES
	Claims		NO
Inventive step (IS)	Claims	3,11	YES
	Claims	1,2,4-10,12-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1. This report makes reference to the following documents:

D1: WO 00/51621 A (EPIGENESIS PHARMACEUTICALS, INC; NYCE, JONATHAN, W) 8 September 2000 (2000-09-08)

D2: WO 00/42173 A (UNISEARCH LIMITED; JOHNSON & JOHNSON RESEARCH PTY. LTD; ATKINS, DAVID) 20 July 2000 (2000-07-20)

D3: WO 01/11023 A (JOHNSON & JOHNSON RESEARCH PTY LTD; UNISEARCH LIMITED; HANDEL, MALCOLM) 15 February 2001 (2001-02-15)

D4: SANTORDO S W ET AL: "A GENERAL PURPOSE RNA-CLEAVING DNA ENZYME" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, Vol. 94, April 1997 (1997-04), pages 4262-4266, XP001009844 ISSN: 0027-8424

D5: SUN L Q ET AL: "Catalytic nucleic acids: From lab to applications" September 2000 (2000-09),

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

PHARMACOLOGICAL REVIEWS, WILLIAMS AND WILKINS INC., BALTIMORE, MD, US, PAGE(S) 325-347, XP002272275 ISSN: 0031 6997

D6: IMAGAWA S ET AL: "NEGATIVE REGULATION OF THE ERYTHROPOIETIN GENE EXPRESSION BY THE GATA TRANSCRIPTION FACTORS" 15 February 1997 (1997-02-15), BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, PAGE(S) 1430-1439, XP000965159 ISSN: 0006-4971

This report is based on claims 1-16, which represent two groups of inventions.

D2 describes DNAzymes against the transcription factor Egr-1 and their therapeutic use.

D3 describes DNAzymes against the transcription factor NF-kappaB and their therapeutic use.

D4 discloses a 15-mer oligodeoxynucleotide having the catayltic potential of a generally usable DNAzyme.

D5 provides a summary of catalytic RNA and DNA molecules and their therapeutic use.

D6 relates to the inhibition of the transcription factors GATA-1, 2, und 3 by means of antisense oligonucleotides.

In view of the documents cited in the search report,

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

the following opinion has been established:

I. First group of inventions: claims 1-8 relate to a method

In D6, GATA-3 was alredy selected as a target and inhibited by means of antisense oligonucleotides. Document D6, in conjunction with, for example, D5, which describes the potential of DNAzymes, provides a person skilled in the art with the information that GATA-3 can be specifically inhibited and that this can be achieved using various means. DNAzymes can therefore be regarded as equivalents that a person skilled in the art would have taken into consideration in order to inhibit GATA-3 mRNA. Therefore, an inventive step cannot be recognized for the general claim 2. This also applies to dependent claims 4-8, since D5 already discloses a stabilization of the DNAzymes (see figure 5). The specific DNAzyme according to claim 3 is regarded as involving an inventive step because, of all of the DNAzymes tested, only this one demonstrated *in vivo* activity. As regards the method according to claim 1, it must be restricted to the DNAzyme according to claim 3. Therefore, objections have been raised under PCT Article 33(3) with respect to claims 1, 2, and 4-8.

II. Second group of inventions: claims 9-16 relate to a method for producing a drug for treating chronic inflammations and to DNAzymes that recognize T-bet mRNA.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Analogously to the objections already raised with respect to the first group of inventions, it is not possible in general to recognize an inventive step for generally defined DNAzymes that inhibit a known target. DNAzymes are one of several possibilities from which a person skilled in the art would select if he wished to inhibit a specific mRNA. The specific selection of a DNAzyme that showed a great amount of activity among other molecules in the *in vivo* test is regarded as inventive (claim 11) since, even today, the criteria for the successful selection of a DNAzyme are still not sufficiently well known.

Therefore, claims 9,10, and 12-16 are not inventive within the meaning of PCT Article 33(3).

2. The penultimate paragraph of claim 10 erroneously also refers to GATA-3 rather than to t-bet.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

The sequence listing in the description, pages 1-51 as originally filed.

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*